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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	13

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/898,234	HAUPTMANN ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-62 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-62 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 07/511,430 .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-62 are pending in the instant application. Claims 1-13 and 15-35 have been amended as requested by Applicant in Paper Number 8, filed January 29, 2002.

Advisory Information

2. Claim 45 is dependent upon claims 15 or 34, and claim 34 is a dependent claim drawn to a specific amino acid sequence while claim 15 is an independent claim. This is pointed out because the Examiner believes that Applicants may have mistakenly inserted claim number 34 in the claim in place of another claim number.

Information Disclosure Statement

3. The information disclosure statement filed July 27, 2001 (Paper No. 3) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. References 34, 92, 107, 118, 120, 121, 134, 146 and 148 were not supplied. Either a duplicate of another paper or a different paper by the same authors was supplied for these references. Therefore those references have not been considered.

Specification

4. The disclosure is objected to because of the following informalities: On page 6 of the substitute specification filed Jan. 16, 2002, on line 38, Figures "6A-6B" should be "6A-6E" to match the figure. Also, on page 7, Figure "7" should be 7A-7D to match the figure.

Appropriate correction is required.

Claim Objections

5. Claim 49 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 49 is a method claim, but the language at the end of the claim "the nucleic acid molecule **defined** in claim 1" is unclear. The objection will be withdrawn if the nucleic acid sequences should be recited in the claim.

Appropriate correction is required.

Priority

6. This application is a continuation of 09/525,998, which is a division of 08/383,676, now patent 6,294,352, which is a continuation of 08/153,287, which is a continuation of 07/821,750, which is a division of 07/511,430. The Examiner notes that certified copies of the German priority documents P39 13 101.7, P3290 282.8 and European priority document 90106624.1 are present in the parent file 07/511,430. However, Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38F.3d551,32 USPQ 2d 1077 (Fed. Cir. 1994). The first priority document, 39 13 101.7, filed April 21, 1989, contains only fragments of the claimed

polypeptides. The second priority document, 3920 282.8, filed June 21, 1989, discloses a polypeptide comprising amino acids 1-371 of the amino acid sequence of the full-length polypeptide of SEQ ID NO: 2. The third foreign priority document, 90106624.2, filed April 6, 1990, discloses the entire amino acid sequence of SEQ ID NO: 2 (455 amino acids). SEQ ID NOS: 4, 6, 8, 10, 12, 14, 16, 18 and 20 are contained within the first 172 amino acids of SEQ ID NO: 2, therefore the priority date accorded to those sequences is June 21, 1989. However, the priority date for the full length protein of SEQ ID NO: 2 is April 6, 1990.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-62 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-59 of copending Application No. 09/899,429. Although the conflicting claims are not identical because Applicantion No. 09/899,429 recites the limitation "wherein said polypeptide is not associated with human urinary proteins", they are not patentably distinct from each other because this limitation is not a true limitation, since the proteins in both applications are recombinantly

produced and would not be associated with urinary proteins, and the methods of treatment are with the same proteins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 15-22 and 45-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8.1 Claims 15-22, 45-48 and 50-62 are indefinite because the "at least one" language of the claims does not place an upper limit on the extent of the changes to be made. For example, as written, it may be possible to make conservative amino acid substitutions at every amino acid residue and still bind TNF, but the protein would be completely different from those of the recited SEQ ID NOS. Therefore, the claims fail to adequately point out that which Applicant sees as the invention.

8.2 Claim 49 is indefinite because it encompasses a method using a protein encoded by a nucleic acid molecule which hybridizes under "**moderately or highly stringent**" conditions, and there are no hybridization conditions defined in the specification. The term "**moderately or highly stringent**" is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 15-22, 37-40, 43-48 and 50-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a polypeptide comprising the amino acid sequence of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 identified as TNF receptor, does not reasonably provide enablement for making and using polypeptides that have at least one conservative amino acid substitution, substitution at a glycosylation site, substitution at a proteolytic cleavage site, substitution at a cysteine residue, amino acid deletion, insertion, or combinations of the above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification discloses a naturally occurring human TNF receptor polypeptide comprising the amino acid sequence presented in SEQ ID NO: 2. This 455 amino acid residue protein is the full length protein, and the specification teaches truncation variants (SEQ ID NOS: 4, 6, 8, 10, 12, 14, 16, 18 and 20) that are soluble and can bind TNF. The soluble form of the TNF receptor is amino acids 20-180 of SEQ ID NO: 2 (The Cytokine Facts Book, Second Edition, Academic Press, Fitzgerald et al. editors, page 478), and all of the disclosed truncation variants contain up to amino acid 201 of SEQ ID NO: 2. The core sequence common to all of the polypeptides is SEQ ID NO: 4, and corresponds to amino acids 41-201 of SEQ ID NO: 2. The core sequence that can therefore bind TNF is amino acids 41-180 of SEQ ID NO: 2. However, because these claims encompass significant structural changes to the protein and truncation variants, a practitioner can not make a protein comprising an amino acid sequence other than the ones disclosed in the instant specification and expect it to have the same

functions. For example, a protein that has at least one conservative amino acid substitution, can have every single amino acid changed, and such a protein would be a completely different protein from the polypeptides disclosed. Claims that encompass a polypeptide with at least one conservatively substituted amino acid residue, or with at least one addition or deletion of amino acid residues to the amino acid sequences, or combinations thereof, encompass proteins which can vary significantly from the disclosed natural sequences. Specifically, the instant specification does not identify those amino acid residues in the amino acid sequence of SEQ ID NO: 4 which are essential for its biological activity and structural integrity and those residues which are either expendable or substitutable. In the absence of this information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis of the amino acid residues before they could even begin to rationally design a functional TNF binding protein having other than a natural amino acid sequence. The disclosure of a natural amino acid core sequence having TNF binding activity is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass all of the other variants encompassed by the claims. The written description is not supportive of the claimed scope of the invention.

The current claim limitations are analogous to those of claim 7 of U.S. Patent Number 4,703,008 which were held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 U.S.P.Q. 2d, 1016 (CAFC, 3/5/91, see page 1026, section D). In that instance, a claim to a nucleic acid encoding a polypeptide having an amino acid sequence sufficiently duplicative of the amino acid sequence of erythropoietin (EPO) so as to have a specified biological activity was held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement. The disclosure upon which that claim was based described a recombinant DNA encoding EPO and a few

analogs thereof. That disclosure differs from the instant specification because, whereas the instant specification describes a human TNF binding protein it does not describe even a single variant thereof, except for the truncation variants. The court held that what is necessary to support claims of this breadth is a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For proteins, that means disclosing how to make and use enough sequences to justify the grant of the claims sought. As indicated, the instant specification is even more limited than the '008 patent because it describes only a single protein and no analogs or mutants thereof and, therefore, provides even less support than the '008 specification for claims of comparable scope and which were held to be invalid in that patent.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

All the Wands factors are considered and it is the balance of factors that determines whether a disclosure enables the use of the invention. It is acknowledged that the level of skill in the art is high. Although the specification on pages 12-16 discusses how variants can be made, the information is of a general nature. There are no working examples of any variants. From the teachings of the specification or the prior art, it is not predictable what changes could be made to the polypeptides that would result in the variants retaining TNF binding activity. For example,

vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836).

For the reasons discussed above, due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples and written description directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

In so far as the claims encompass an isolated protein, other than the only one disclosed in the instant specification which is the human TNF binding protein having the amino acid sequence of SEQ ID NO: 2 and the truncation variants, the written description of the instant specification is not supportive of the claimed scope and does not fulfill the written description requirement of 35 U.S.C. 112, first paragraph.

In the decision of *The Regents of the University of California v. Eli Lilly and Company,* 43 USPQ2d 1398 (CAFC 1997), the court held that:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using

"such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood , 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Because the specification merely discloses one polypeptide sequence, and does not describe any other, the written description requirement has not been met.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 15, 22 and 37-40, 43-49 are rejected under 35 U.S.C. 102(a) as being anticipated by Wallach et al., EP 0 308 378, publication date March 22, 1989 (cited by Applicants).

Claims 15, 22 and 37-40, 43-49 encompass a method of ameliorating the harmful effects of TNF in an animal, comprising administering a polypeptide comprising the amino acid

sequence as set forth in any of SEQ ID NOS: 4, 6, 8, 10, 12, 14, 16, 18 and 20, or fragments thereof, and modified variants thereof, or encoded by a nucleic acid which hybridizes under moderately or highly stringent conditions to the complement of the nucleic acid molecules of claim 1. These amino acid sequences correspond to various truncations of the soluble portion of the full-length TNF binding protein of SEQ ID NO: 2. Wallach et al. teach the purification of a TNF binding protein that is stated by Applicants to be identical to the protein of the claimed invention (see page 8, lines 27-34). The soluble portion of the TNF receptor is from amino acids 1-180 of SEQ ID NO: 2 (The Cytokine Facts Book, Second Edition, Academic Press, Fitzgerald et al. editors, page 478), and the sequences of SEQ ID NOS: 4, 6, 8, 10, 12, 14, 16, 18 and 20 comprise amino acids up to amino acid 201 of SEQ ID NO: 2, so the amino acid sequences of these polypeptides contain 21 more amino acids at the carboxyl terminus than the soluble TNF binding protein of Wallach. However, C-terminal deletions of the polypeptides are therefore encompassed by the disclosure of Wallach et al. The protein of Wallach et al. is encoded by a nucleic acid that would hybridize under moderately or highly stringent conditions to the complement of the nucleic acid molecules of claim 1 because it is it the same protein. Wallach et al. also teach that functional derivatives of the protein can be made that retain TNF binding activity and that active fractions of the TNF inhibitory protein covers any fragment or precursors of the polypeptide chain of the protein (page 4, lines 28-43), and teach that the TNF binding proteins may be used in treating any condition where there is an over production of endogenous TNF, such as in cases of septic shock, cachexia, graft-versus host reactions, autoimmune diseases like rheumatoid arthritis, etc (see page 13, line 1-16). Although the specific amino acid sequences of SEQ ID NOS: 4, 6, 8, 10, 12, 14, 16, 18 and 20 are not taught by Wallach et al., the

amino acid sequence of a protein is an intrinsic property of the protein. Therefore, Wallach et al. anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 15 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson et al., Eur. J. Haematol., March, 1989, Vol. 42, pages 270-275 (cited by Applicants) and further in view of Wallach et al., EP 0 308 378, publication date March 22, 1989.

Claims 15 and 22 encompass a method of ameliorating the harmful effects of TNF in an animal, comprising administering a polypeptide comprising the nucleotide sequence as set forth in any of SEQ ID NOS: 4, 6, 8, 10, 12, 14, 16, 18 and 20, that have at least one amino acid substitution and C-terminal truncation. Olsson et al. teaches the isolation of a TNF binding protein comprising an amino terminal sequence D-S-V-X-P-Q-G-K-Y-I-H-P-Q-V-N-S-I-X-K-T, which differs from the corresponding sequence of SEQ ID NO: 2 by two amino acids. Therefore, TNF binding proteins comprising at least one amino acid substitution and a C-terminal deletion are encompassed by the protein of Olsson et al. Olsson et al. do not teach a method of treatment comprising adminstration of the TNF binding proteins.

Wallach et al. teach that TNF binding proteins may be used in treating any condition where there is an over production of endogenous TNF, such as in cases of septic shock, cachexia,

graft-versus host reactions, autoimmune diseases like rheumatoid arthritis, etc (see page 13, line 1-16).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use the TNF binding proteins of Olsson et al. to treat disorders mediated by TNF, as taught by Wallach et al. The skilled artisan would be motivated to do so to treat diseases or disorders, and there would be a reasonable expectation of success, since use of cytokine inhibitors, such as TNF antibodies, has been widely and successfully used in the field of medicine.

Conclusion

12.1 No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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